REMARKS

Claims 1-3, 6-10, 12-21, 26-28, 31-35 and 37-47 are pending in the instant application. Claims 1-3, 6-10, 12-21, 26-28, 31-35 and 37-47 have been rejected by the Examiner. Reconsideration of the captioned application based on the above amendments and following remarks is respectfully requested.

As a preliminary matter, Applicants would like to thank the Examiner for the telephonic interview of September 11, 2006, intended to advance the prosecution of the instant invention. In accordance with the discussions with the Examiner, Claims 1 and 26 have been amended to recite that the first organic solvent and the second organic solvent are each glyme. Applicants submit that the amendments are fully supported by the specification as filed (see for example, page 13, lines 20-24 and page 17, lines 24-28) and that no new matter is being added. By the above Amendments, Claims 6 and 31 have been canceled without prejudice. After entry of the amendments, Claims 1-3, 7-10, 12-21, 26-28, 32-35 and 37-47 will remain pending and under consideration.

The Examiner has rejected Claims 1-3, 6-10, 12-21, 26-28, 31-35 and 37-47 under 35 U.S.C. §103(a) as allegedly unpatentable over Maryanoff et al. More specifically, the Examiner maintains that Maryanoff et al. disclose:

> the instant 2 step process using THF or TBME as solvents for both steps. Applicants claim the same process except that they are excluded as solvents and because applicants recite that their process is continuous. However it is considered obvious to use other common solvents including glycol-dimethyl ether i.e. glyme, (see claim 6) for both steps in view of Maryanoff's teachings. Conversion of known process to a continuous one is obvious.

Applicants respectfully traverse the rejection. Applicants submit that Maryanoff et al. do not teach or suggest the process of the present invention wherein Step (A) is completed in a first organic solvent which is glyme and Step (B) is completed in a second organic solvent which is also glyme.

Maryanoff et al., in US Patent 5,387,700, teach reacting an alcohol of formula RCH_2OH with sulfuryl chloride in the presence of a base, in a solvent selected from the group consisting of toluene, t-butyl methyl ether or tetrahydrofuran to yield the compound of formula RCH_2SO_2Cl; and then reacting the compound of formula RCH_2SO_2Cl with an amine in a solvent selected from the group consisting of tetrahydrofuran, t-butyl methyl ether and lower alcohol (e.g. methanol or ethanol). Maryanoff et al. do not teach or suggest that the reaction steps may be run in any ether or hydrocarbon (i.e. any member of the class of solvents known as ethers or hydrocarbons), but rather Maryanoff et al. call out specific examples of suitable solvents. Further, Maryanoff et al., in the Examples and specification, suggest that the preferred solvent of the first step is toluene (a hydrocarbon) and the preferred solvent of the second step is tetrahydrofuran (a cyclic ether). Thus, Maryanoff et al. suggest that the preferred solvent for the first and second steps are different (*see, e.g.*, column 2, line 55 through column 3, line 25), and neither of these solvents preferred by Maryanoff et al. are encompassed within the instant claims, as amended. Additionally, Maryanoff et al. do not teach or suggest the use of glyme in either step, regardless of whether the process is run in a batch or continuous mode.

Applicants further submit that the choice of solvent for the first and second steps of the continuous process of the present invention would not be obvious to one skilled in the art in view of the disclosure of solvents suitable for the two steps in a batch process. Applicants submit that for a solvent to be suitable for a continuous process, said solvent must meet criteria which are often different and greater in number than those required for a batch process. For the two step continuous process of the present invention, a suitable solvent must for example: (a) provide appropriate solubility for the starting materials, reagents, intermediates and products for both steps; (b) be inert to the starting materials, reagents, intermediates and products for both steps; (c) be compatible with the temperature, pressure and other reaction conditions of both steps as run in continuous reactors (which may be different from those used in batch reactors); and (d) provide reaction rates which yield product within reasonable

continuous reactor residence time. Thus, Applicants maintain that the choice of suitable solvents for a continuous process would not be obvious based on a teaching of solvents which would be suitable for a batch process.

Experiments were completed by the Applicants to identify solvents which are suitable for the continuous processes of the present invention, as applied to the preparation of topiramate. More specifically, representative solvents were evaluated for their effect on the yield, purity and rate of reaction for preparation of the intermediate chlorosulfate and the final product topiramate.

For Step (A) of the continuous processes of the present invention, glyme, THF, MTBE, toluene (the preferred solvent for Step (A) as disclosed in Maryanoff et al.) and neat conditions (i.e. in pyridine) were considered. Glyme, MTBE and toluene were determined to be suitable solvents for Step (A), with relatively fast reaction rates and good yields of chlorosulfate product. By contrast, THF and neat (in pyridine) conditions were determined to be unsuitable for Step (A) because mixing sulfuryl chloride with THF resulted in a vigorous exotherm which is incompatible with continuous process manufacture, and further, because under neat (in pyridine) conditions, the reaction rate was relatively slow.

For Step (B) of the continuous processes of the present invention, the following solvents were evaluated for suitability with respect to product purity, reaction times and formation of by-products (including diacetone-β-D-fructose (DAF) starting materials): MTBE, glyme, diglyme, toluene, THF (the preferred solvent for Step (A) as disclosed in Maryanoff et al.) and a mixture of THF and toluene. MTBE was determined to be unsuitable for Step (B) of the continuous process, because the rate of reaction was relatively slow and because in this solvent, the reaction produced significant amounts of the starting material DAF as a by-product. Similarly, toluene resulted in relatively poor yields, high levels of starting material DAF by-product and poor reagent solubilities; while THF: toluene mixtures resulted in relatively low product yields and relatively slow reaction times, requiring reaction times on the order of days to reach completion. THF

was determined to be suitable for Step (B), but as discussed above, was not suitable for Step (A). Only glyme and diglyme produced relatively fast reaction rates and good selectivity for conversion of the chlorosulfate intermediate to topiramate product (i.e. relatively high product yields), with relatively low starting material DAF by-product formation.

Applicants submit that the results of the experiments discussed above indicate that solvents which are suitable for Step (A) of the instant two step continuous process are not necessarily suitable for Step (B) of the instant two-step continuous process and vice versa, and further, that glyme was a suitable choice for both steps in a continuous process. Thus, Applicants submit that the choice of solvent(s) suitable for both steps of the instant two-step continuous process would not be obvious to one skilled in the art in view of the teachings of solvents suitable for the corresponding batch process. Additionally, Applicants submit that the determination of the effect of solvent on reaction parameters (including for example reaction rate and selectivity) and therefore the determination or selection of suitable solvent(s) would not be within the scope of standard experimentation.

Applicants therefore maintain that the teachings of Maryanoff et al. do not teach or suggest the continuous processes of the present invention, wherein Step (A) is completed in a first organic solvent which is glyme and Step (B) is completed in a second organic solvent which is also glyme.

Applicants further submit that a continuous process is one wherein the reactant(s) are introduced and the product(s) withdrawn in an uninterrupted manner (except for interruptions related to start-up, maintenance, or for scheduled shut down periods). By contrast, a batch process is one where all the reactants are added to the reactor and then processed according to a predetermined course of reaction during which no material is continuously fed into or removed from the reactor. Applicants maintain that Maryanoff et al., in US Patent 5,387,700, do not teach or suggest the continuous process of the present invention, nor do Maryanoff et al. teach or suggest a

process wherein Step (A) is completed in a first organic solvent which is glyme and Step (B) is completed in a second organic solvent which is also glyme. Rather, Maryanoff et al., in US Patent 5,387,700, in the Examples and specification, suggest the preferred solvent of the first step (toluene) and the preferred solvent of the second step (THF) are different (*see, e.g.*, column 2, line 55 through column 3, line 25).

Applicants submit that although it may be desirable to make a process continuous, it does not necessarily and inevitably follow that a batch process can be run in a continuous manner. Applicants submit that it does not necessarily follow that a batch process can be converted to the corresponding continuous process by simply running the batch process step(s) in a continuous manner. Firstly, as discussed in detail above, the solvents which are suitable in a batch process are not necessarily suitable in a continuous process because of the added compatibility criteria. Additionally, process conditions, including for example, the rate of addition of reagents, reaction temperature, pressure, etc., may need to be adjusted to maximize product yield within the parameters of the continuous process residence time. Further, the process and / or process conditions may need to be adjusted to permit continuous handling (streaming) of the intermediates, products and impurities / by-products. Applicants maintain that said process condition selections are not obvious and further are not within the scope of standard experimentation. Applicants therefore maintain that it would not be obvious to one skilled in the art how to convert the batch process as disclosed in Maryanoff et al. to a continuous process.

Applicants further submit that, at most, the teaching in Maryanoff et al, US Patent 5,387,700, might make it obvious to try to run the 2-step process disclosed therein in a continuous manner. However, obvious to try is an improper basis for a § 103(a) rejection when there is no suggestion or expressed expectation of success in the prior art that would have led one to perform the experimentation in the first place. Although obviousness does not require absolute predictability, a reasonable expectation of success is necessary. Applicants urge that in the instant case, there was no reasonable

expectation of success that the 2-step process disclosed in Maryanoff et al. could be run in a continuous manner.

In view of the above amendments and remarks, Applicants submit that the present invention is not obvious in view of Maryanoff et al., US Patent 5,387,700, and Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3, 7-10, 12-21, 26-28, 32-35 and 37-47 under 35 U.S.C. §103(a). Accordingly, Applicants maintain that the application is in condition for allowance and Applicants respectfully request allowance of the pending claims.

Respectfully submitted,

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